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(54) Title: POTASSIUM SALT OF (*S*)-OMEPRAZOLE

(57) Abstract

The present invention relates to a novel form of 5- methoxy- 2- [[(4- methoxy- 3,5- dimethyl- 2- pyridinyl) methyl] sulfinyl] -1H- benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (*S*)- enantiomer of 5- methoxy- 2- [[(4- methoxy- 3,5- dimethyl- 2- pyridinyl) methyl] sulfinyl] -1H- benzimidazole. The present invention also relates to processes for preparing such a form of the potassium salt of (*S*)- omeprazole and pharmaceutical compositions containing it.

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POTASSIUM SALT OF (*S*)-OMEPRAZOLE

Field of the invention

The present invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (*S*)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.The present invention also relates to a process for preparing such a form of potassium salt of (*S*)-omeprazole and pharmaceutical compositions containing it.

Background of the invention and prior art

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom is the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (*R*)- and (*S*)-enantiomer of omeprazole, herein referred to as (*R*)-omeprazole and (*S*)-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt

form were found to have *R* and *S* configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of the single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and structually related compounds as well as salts thereof. WO 96/01623 discloses pharmaceutical dosage forms comprising for instance magnesium salts of (*R*)- and (*S*)-omeprazole.

WO 98/54171 discloses a process for the preparation of the trihydrate of magnesium salt of (*S*)-omeprazole, wherein the potassium salt of (*S*)-omeprazole is used as an intermediate. The potassium salt of (*S*)-omeprazole, according to the prior art, crystallizes as a methanol solvate.

Certain salts of of (*S*)-omeprazole, such as the potassium salt, are in general suitable compounds for i.v.-administration due to their intrinsic properties, such as high stability and high solubility in water. Methanol solvates are however not suitable for i.v.-administration, since the concomitant administration of methanol could be fatal for the receiver. Therefore there exists a need for a potassium salt of (*S*)-omeprazol that is free from methanol.

The novel form of the potassium salt of (*S*)-omeprazole according to the present invention is hereinafter referred to as the potassium salt of (*S*)-omeprazole form B. The prior art form of the potassium salt of (*S*)-omeprazole disclosed in WO 98/54171 is hereinafter referred to as the potassium salt of (*S*)-omeprazole form A.

Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of the potassium salt of (*S*)-omeprazole prepared according to the present invention, i.e. form B.

Figure 2 is an X-ray powder diffractogram of the potassium salt of (*S*)-omeprazole prepared according to example 2 in WO 98/54171, i.e. form A.

Description of the invention

It has surprisingly been found that the potassium salt of (*S*)-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure potassium salt of (*S*)-omeprazole form B.

The potassium salt of (*S*)-omeprazole form B is advantageous because it is hydrate form, while the previous known form A is methanol solvate. The potassium salt of (*S*)-omeprazole form B is especially suitable for intravenous administration. The potassium salt of (*S*)-omeprazole form B is further characterized by being crystalline, and preferably being highly crystalline.

The potassium salt of (*S*)-omeprazole form B, obtained according to the present invention, is substantially free from other forms of potassium salts of (*S*)-omeprazole, such as the corresponding form A described in the prior art .The potassium salt of (*S*)-omeprazole form B obtained according to the present invention is also substantially free from potassium salts of (*R*)-omeprazole.

The potassium salt of (*S*)-omeprazole form B is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram , but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other forms of potassium salt of (*S*)-omeprazole and accordingly, the potassium salt

of (*S*)-omeprazole form B is easily distinguishable from any other crystal forms of potassium salts of (*S*)-omeprazole disclosed in prior art. With the expression "any form" is meant anhydrates, hydrates, solvates, amorphous forms, and polymorphs. Such examples of any forms of potassium salt of (*S*)-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, amorphous forms and polymorphs.

The potassium salt of (*S*)-omeprazole form B may also be characterized by its unit cell.

In a further aspect, the present invention provides a process for the preparation of the potassium salt of (*S*)-omeprazole form B which comprises the step of converting (*S*)-omeprazole into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, such as potassium hydroxide or potassium methylate, followed by isolation of the formed salt.

The crude (*S*)-omeprazole used in the process can for example be prepared by oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole into (*S*)-omeprazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent, such as toluene or dichloromethane, as is described in the prior art, see WO 98/54171.

The potassium salt of (*S*)-omeprazole form B, prepared according to the present invention is analyzed, characterized and differentiated from the previous known form A by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate the potassium salt of (*S*)-omeprazole form B from the corresponding form A is by conventional FT-IR.

The amount of water in the potassium salt of (*S*)-omeprazole form B is determined by thermogravimetric analysis (TGA), a technique which is known per se.

The potassium salt of (*S*)-omeprazole form B is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on non-steroidal anti-inflammatory drug (NSAID) therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The potassium salt of (*S*)-omeprazole form B may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the potassium salt of (*S*)-omeprazole form B may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The potassium salt of (*S*)-omeprazole form B may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the potassium salt of (*S*)-omeprazole form B, according to the present invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like. The potassium salt of (*S*)-omeprazole form B is, because of being highly soluble in water, especially suitable for parenteral formulations, such as i.v.

According to the invention there is further provided a pharmaceutical composition comprising the potassium salt of (*S*)-omeprazole form B, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of the potassium salt of (*S*)-omeprazole form B in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of

treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the potassium salt of (*S*)-omeprazole form B.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the potassium salt of (*S*)-omeprazole form B in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable dosage form may cover a dose range from 5 mg to 120 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 5 mg to 100 mg, and more preferred 10 mg to 80 mg. A suitable administration dose is 20 mg to 40 mg for intravenous administration as well as oral administration

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques. Especially suitable oral formulations are described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination therapies comprising the potassium salt of (*S*)-omeprazole form B and other active ingredients in separate dosage forms may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, *i.e.* the potassium salt of (*S*)-omeprazole form B, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

Examples

Potassium salt of (S)-omeprazole form B

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (67 mmol) in toluene (4 mL/g 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole) was charged with water (0,9 mmol) and D-(-)-diethyl tartrate (14 mmol) at 50°C. After stirring for 20 minutes, titanium(IV) isopropoxide (6,5 mmol) was added and the solution was stirred for approximately 50 minutes. The reaction mixture was temperated to 35°C and N,N-diisopropylethylamine (10 mmol) was added. Cumene hydroperoxide (74 mmol) was then charged to the solution while keeping the temperature at approximately 35°C.

After 3 hours, the reaction mixture was diluted with toluene (2 mL/g 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole) and potassium methoxide (26 mmol) was added as a slurry in toluene (8 mL/g KOMe).
The obtained crystals were filtered off and dried (36°C, vacuum) over night.
Yield 0,72 g (1,9 mmol; 7 % in respect of KOMe).

Content of solvents as obtained with Karl-Fischer titration and GC respectively (% w/w)

Water 3,4

Methanol 0,01

TGA

Approximately 2 % (w/w) of the water content is incorporated in the crystal lattice (*i.e.* ~0,5 H_2O / molecule of potassium salt of (*S*)-omeprazole form B)

XRD

The X-ray powder diffractogram of the product measured from 1-40° in 2θ with $CuK\alpha_1$ radiation shows the following characteristic list of peaks:

d-value [Å]	*Intensity*
9.6	very strong
8.0	strong
7.9	strong
7.5	weak
7.3	weak
7.2	very strong
5.9	strong
5.6	strong
5.2	strong
5.1	very strong
4.88	weak
4.83	weak
4.71	weak
4.67	weak
4.55	medium
4.49	strong
4.39	strong
4.15	weak

d-value [Å]	*Intensity*
4.10	weak
3.95	weak
3.74	very strong
3.67	medium
3.58	strong
3.55	medium
3.47	strong
3.40	weak
3.27	strong
3.20	medium
3.15	medium
3.10	weak
3.03	weak
2.98	medium
2.87	medium
2.85	medium
2.38	medium
2.30	weak

In addition the diffractogram contains several weak peaks that have been omitted for clarity.

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the potassium salt of (*S*)-omeprazole form B. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)

CLAIMS

1. The potassium salt of (*S*)-omeprazole form B, characterized in being a hydrate form.

2. The potassium salt of (*S*)-omeprazole form B according to claim 1, characterized in being crystalline.

3. The potassium salt of (*S*)-omeprazole form B, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

d-value [Å]	*Intensity*
9.6	very strong
8.0	strong
7.9	strong
7.5	weak
7.3	weak
7.2	very strong
5.9	strong
5.6	strong
5.2	strong
5.1	very strong
4.88	weak
4.83	weak
4.71	weak
4.67	weak
4.55	medium
4.49	strong
4.39	strong
4.15	weak

d-value [Å]	*Intensity*
4.10	weak
3.95	weak
3.74	very strong
3.67	medium
3.58	strong
3.55	medium
3.47	strong
3.40	weak
3.27	strong
3.20	medium
3.15	medium
3.10	weak
3.03	weak
2.98	medium
2.87	medium
2.85	medium
2.38	medium
2.30	weak

4. A process for the preparation of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, which comprises the step of converting (*S*)-omeprazole into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, such as potassium hydroxide or potassium methylate, followed by isolation of the formed salt.

5. A process according to claim 4, comprising the additional step of oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent, such as toluene or dichloromethane, to obtain (*S*)-omeprazole

6. A pharmaceutical formulation comprising the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in admixture with a pharmaceutically acceptable excipient.

7. A pharmaceutical formulation suitable for i.v. administration comprising the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in admixture with a pharmaceutically acceptable excipient.

8. The use of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

9. The use of the potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3 in the manufacture of a pharmaceutical formulation for i.v. administration.

10. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of potassium salt of (*S*)-omeprazole form B as defined in any of claims 1-3, to a patient suffering from gastrointestinal disorders.

Fig. 1

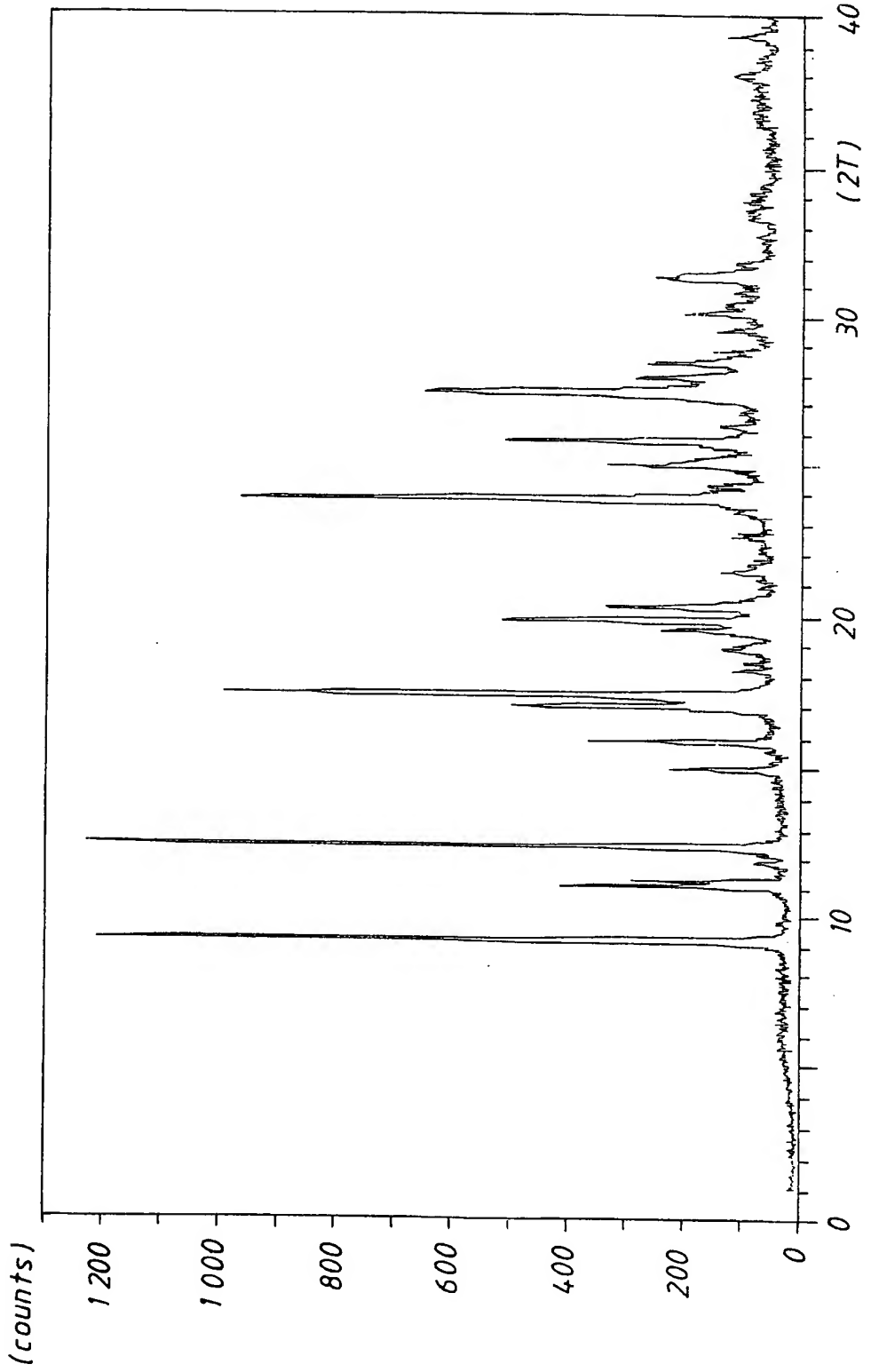
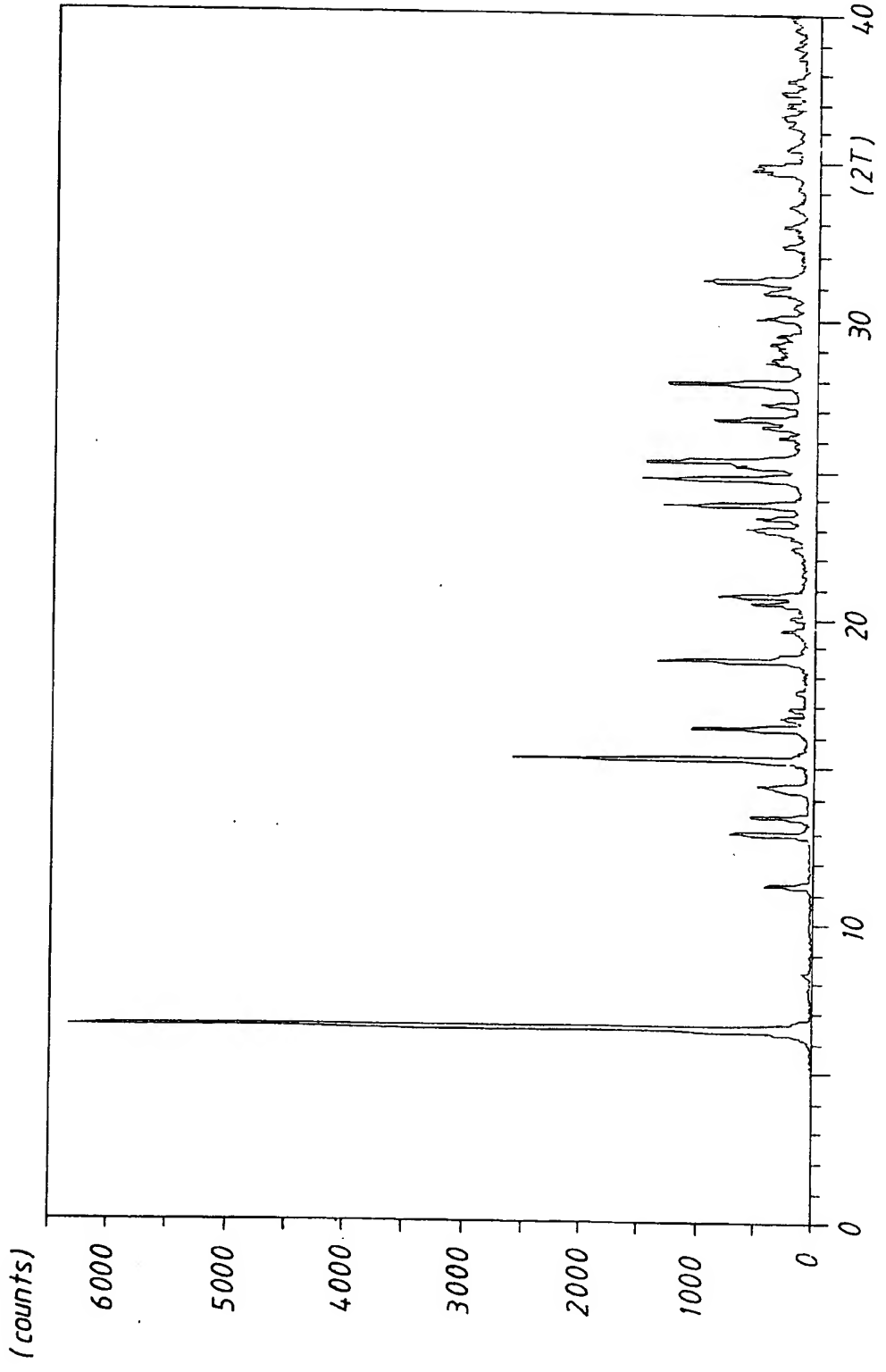


Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00087

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9854171 A1 (ASTRA AKTIEBOLAG), 3 December 1998 (03.12.98) --	1-9
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.94) -- --------	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2000	19 -05- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/0087

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

02/12/99

International application No.
PCT/SE 00/00087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9854171 A1	03/12/98	AU 7793598 A	30/12/98
		AU 7849898 A	03/07/98
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